**PATENT**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

Applicants:

**PETER L. OREN ET AL.**

Serial No.: 10/031,464

Filed: April 29, 2002

For: **β-CARBOLINE PHARMACEUTICAL COMPOSITIONS**

Attorney Docket No. 29342/36230A

Group Art Unit: 1615

Examiner: L. Channavajjala

I hereby certify that this paper is being deposited with the United States Postal Service with sufficient postage, as first class mail, in an envelope addressed to: Commissioner for Patents P.O. Box 1450 Alexandria, VA 22313-1450

Dated: **December 21, 2005**

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**DECLARATION OF MARTHA A. KRAL UNDER 37 C.F.R. §1.132**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

NOW COMES MARTHA A. KRAL, Declarant herein, and states as follows:

1. I am a coinventor of the invention disclosed and claimed in the above-identified patent application.

2. I am presently employed by Eli Lilly and Company, Indianapolis, IN. My present title is Research Advisor. I have been employed by Eli Lilly and Company since 1998, engaged in product development and technical support of pharmaceutical formulations.

3. Previous to my employment at Eli Lilly and Company, I was employed at Hoechst Marion Roussel Inc., and the predecessor company, Marion Merrell Dow, Inc., Kansas City, MO from 1992 to 1998, providing technical support and developing pharmaceuticals and bioproducts. Prior to transferring to Kansas City, MO, I was employed at Marion Merrell Dow, and the predecessor company Merrell Dow, Cincinnati, OH from 1989 to 1992 in pharmaceutical research.

4. I have earned a B.A. in Biology (1975), and an M.S. (1985) and a Ph.D. (1990) in Pharmaceutical Chemistry, all from the University of Kansas, Lawrence, KS.

5. Throughout my academic and professional careers, I conducted research in the pharmaceutical arts and helped develop formulations for commercial drug products. I am a member of the American Associate of Pharmaceutical Scientists (AAPS).

6. I have read and understand the Office Action dated September 21, 2005, which was issued in connection with U.S. Patent Application Serial No. 10/031,464. I also have read and understand the following references cited by the examiner in U.S.S.N. 10/031,464:

WO 97/03675 (WO '675);
WO 96/38131 (WO '131); and
Seth et al. U.S. Patent No. 4,721,709 ('709).

7. Pending claims 1-4, 6-16, 18-25, and 28-36 of U.S.S.N. 10/031,464 were rejected as being obvious over a combination of the WO '675, WO '131, and '709 references because

> "[D]uang [sic] teaches the claimed beta-carboline compounds and compositions containing the compounds, as also acknowledged by applicants on page 2 of the instant application. Daung [sic] specifically discloses teaches [sic] instant preferred compound (instant specification, page 3, lines 28-30) for treating conditions where inhibition of PDE5 is beneficial (see page 3, lines 24-25, lines 30-32 and is also referred to as compound A). On page 12, lines 11-12, Daung [sic] teaches that the compounds a [sic] and B are prepared as different dosage forms and in particular, Table B shows a tablet prepared by wet granulation, where in the tablet composition contains beta-carboline drug as active agent and other excipients such as polyvinylpyrrolidone, PEG, Polysorbate 80, magnesium stearate, cross-caramellose [sic] sodium, and microcrystalline cellulose, which read on the instant claimed binder, diluent, wetting agent, lubricant and disintegrant respectively. Instant dependent claims specifically recite the excipients of Table B of Daung [sic]. With respect to the percentages of active ingredients and the excipients claimed, the total weight of the composition of tablet in Table B is 500 mg. A calculation of the proportion of each ingredient in Table 2 reads on the instant claimed percentages. With respect to the claimed 'free drug', Daung [sic] does not teach an intimately embedded drug in a polymeric co-precipitate and hence meets the definition of 'free drug' (instant page 5, lines 24-27). Instead, Daung [sic] only teaches direct compression or wet granulation followed by compression to prepare the tablets (pages 12-14)." (Office Action of September 21, 2005, pages 2 and 3).

Various dependent claims are rejected based on a contention that the claimed percentages of diluents and

particle sizes are optimizations within the "scope of a skilled artisan."

8. Based on my training and experience, the pending claims would not have been obvious to a person of ordinary skill over a combination of WO '675, WO '131, and the '709 patent. The claimed invention is directed to pharmaceutical formulations, which exhibit unexpected and surprising results in the therapeutic delivery of Compound A through enhanced bioavailability. Compound A is identified at page 7, lines 21-28 of the specification. As a result, the claimed formulations achieve a rapid onset of the therapeutic effect, which has been identified as a problem involving the beta-carboline compounds, as well as providing tablets with uniform potency and desirable stability.

9. We prepared tablets and performed tests to assess two of the examples (A2 and B2) disclosed in WO '675 and to compare those examples to the claimed formulations. Example B1 of WO '675 utilizes a nonconventional manufacturing process that includes granulation of the active ingredient, drying, and extrusion at elevated temperatures and pressures. The excipients taught in the WO '675 B1 example include 10% PEG as a binder, which at that level is known to potentially prolong the disintegration time of tablets. When excipients in the B1 example are manufactured by the described process, a thermoplastic granulation is produced. This type of process is typically used to prepare dosage forms that are meant to dissolve slowly, such as lozenges. These tablet properties would not solve the problem that our invention overcomes,

specifically, rapid dissolution to achieve rapid onset of action and enhanced bioavailability. Thus, the Daugan B1 example teaches neither a workable nor a practicable formulation and process.

10. Example A2, a direct compression formulation, and Example B2, a wet granulation formulation, of WO '675 were manufactured as 10 mg tablets, rather than 50 mg tablets, because this dosage is one of the preferred tablet strengths. The formulations of these examples were manufactured at a laboratory scale of 15,000 to 18,000 tablets, and were adjusted for the decrease in the percent loading of Compound A by an equal increase in the percent loading of one excipient, i.e., microcrystalline cellulose in Example A2 and lactose in Example B2. The same lot of Compound A, which contained a small particle size as recited in claim 1 of the application, was used in all formulations discussed herein. Based on my training and experience, the 50 mg tablets in Examples A2 and B2 disclosed in WO '675 would be expected to exhibit similar tablet properties as the 10 mg tablets manufactured because the adjustment of the formulas is slight. These unit formulas are provided in Tables 1 and 2 below.

11. Table 1 provides the unit formulas for the 50 mg tablets disclosed in Example A2 of WO '675 and the 10 mg tablets manufactured by direct compression.

| Table 1. Unit Formula Comparison of WO '675 Example A2 | | | | |
|---|---|---|---|---|
| | WO '675 Example A2 (50 mg) | | Applicant Example A2 (10 mg) | |
| **Ingredient** | **mg/tablet** | **% w/w of core tablet** | **mg/tablet** | **% w/w of core tablet** |
| Active Ingredient (Compound A) | 50.0 | 25.00 | 10.0 | 5.00 |
| Colloidal Silicon Dioxide | 0.5 | 0.25 | 0.5 | 0.25 |
| Crospovidone | 8.0 | 4.00 | 8.0 | 4.00 |
| Sodium Lauryl Sulfate | 1.0 | 0.50 | 1.0 | 0.50 |
| Magnesium Stearate | 1.0 | 0.50 | 1.0 | 0.50 |
| Microcrystalline Cellulose | 139.5 | 69.75 | 179.5 | 89.75 |
| **Total core tablet** | 200.0 | 100.00 | 200.0 | 100.00 |

12. Table 2 provides the unit formulas for the 50 mg tablets disclosed in Example B2 of WO '675 and the 10 mg tablets manufactured by wet granulation.

| Table 2. Unit Formula Comparison of WO '675 Example B2 | | | | |
|---|---|---|---|---|
| | WO '675 Example B2 (50 mg) | | Applicant Example B2 (10 mg) | |
| **Ingredient** | **mg/tablet** | **% w/w of core tablet** | **mg/tablet** | **% w/w of core tablet** |
| Active Ingredient (Compound A) | 50.0 | 16.67 | 10.0 | 4.00 |
| Polysorbate 80 | 3.0 | 1.00 | 2.5 | 1.00 |
| Lactose | 178.0 | 59.33 | 180.0 | 72.00 |
| Starch | 45.0 | 15.00 | 37.5 | 15.00 |
| Pregelatinized Starch | 22.5 | 7.50 | 18.75 | 7.50 |
| Magnesium Stearate | 1.5 | 0.50 | 1.25 | 0.5 |
| **Total core tablet** | 300.0 | 100.00 | 250.00 | 100.00 |

13. The tablets manufactured by direct compression based on Example A2 of WO '675 were extremely hard (about 23 kp) and failed to release a sufficient amount of the drug during dissolution testing to be acceptable. In other words, the dissolution of the

free drug particles of Compound A from the tablet is incomplete, indicating that the formulation is inherently the cause of the low dissolution.

14. Seth (WO '709) discloses in Column 1, lines 66 - 68 and Column 2, lines 1 - 20 that a frequently used method to overcome the slow rate of dissolution of poorly soluble, hydrophobic drugs is to finely grind or 'micronise' drug substances so as to reduce their particle size. A major disadvantage of such grinding methods is the resulting tendency of the milled particles to agglomerate and the formation of an electrostatic charge on their surfaces which leads to poor flow and wetting of the particles. Seth taught that these problems could be overcome by adsorbing a hydrophobic, poorly soluble drug to a pharmaceutical carrier (Column 4, lines 44 - 48). However, Seth did not teach nor suggest how to utilize micronised free drug to improve bioavailability without adsorbing the drug to the carrier. Surprisingly, our invention was able to use micronised free drug without adsorbing the drug on to a carrier to achieve uniform potency, rapid absorption, and improved bioavailability.

15. The tablets manufactured by wet granulation based on Example B2 of WO '675 dissolved very quickly. However, these tablets were so soft (about 2 kp) that they were not sufficiently robust for a further manufacturing step, such as film coating, without significant breakage or erosion.

16. To solve the above problems of unacceptably low tablet dissolution and insufficient tablet hardness, the formulations of the present invention were developed based on many experiments to find the

proper combination and quantities of excipients to provide physically robust tablets that also released the drug quickly and completely. The removal of starch to obtain acceptable tablets was not taught by Daugan, and several additional changes to the formulation, as discussed below, were required to produce tablets with the appropriate properties. To illustrate the advantages of the presently claimed formulation, the 10 mg formula of Example 1 of the present specification is provided in Table 3.

**Table 3. Unit Formula for 10 mg Tablet (Example 1)**

| Ingredient | mg/tablet | % w/w of core tablet |
|---|---|---|
| **Granulation** | | |
| Active Ingredient (Compound A) | 10.0 | 4.00 |
| Lactose Monohydrate | 153.8 | 61.52 |
| Spray Dried Lactose Monohydrate | 25.0 | 10.00 |
| Hydroxypropyl Cellulose | 4.0 | 1.60 |
| Croscarmellose Sodium | 9.0 | 3.60 |
| Hydroxypropyl Cellulose (EF) | 1.75 | 0.70 |
| Sodium Lauryl Sulfate | 0.7 | 0.28 |
| **Outside Powders** | | |
| Microcrystalline Cellulose | 37.5 | 15.00 |
| Croscarmellose Sodium | 7.0 | 2.80 |
| Magnesium Stearate | 1.25 | 0.50 |
| **Total core tablet** | 250.0 | 100.00 |

The 10 mg tablets were manufactured at a laboratory scale (18,000 tablets). The use of a water-soluble diluent, i.e., lactose monohydrate, with a hydrophilic cellulosic binder (hydroxypropylcellulose), provided a good granulation. The addition of spray dried lactose monohydrate enhanced the compressibility of the final granulation, as did the outside powder addition of microcrystalline cellulose, resulting in tablets that were sufficiently hard to withstand the coating process, packaging, and shipping.

17. The tablets prepared according to Table 3 disintegrated and dissolved rapidly to meet the therapeutic need for rapid onset of Compound A. WO '675 fails to teach or suggest that modifying the level of microcrystalline cellulose, or removing the relatively small quantities of water insoluble starch (22.5% of the tablet) and using only water soluble lactose in the granulation would significantly improve tablet hardness. Surprisingly, the present formulation solved the above-mentioned problems and produced tablets that not only provide a rapid therapeutic onset, but also are stable and achieve good bioavailability.

18. Table 4 summarizes the compressibility of the three granulation compositions provided in Tables 1 to 3, as measured by tablet hardness in kiloponds (kp), at various tablet press compression forces.

**Table 4. Tablet Hardness Values as a Function of Compression Force**

| Compression Force (kg) | Hardness (kp) | | |
|---|---|---|---|
| | WO '675 A2 (10 mg) | WO '675 B2 (10 mg) | Example 1 (10 mg) |
| 1100 | 22.9 | 1.4 | 6.6 |
| 1600 | 23.5 | 2.1 | 9.6 |
| 1800 | 23.2 | 2.3 | 9.0 |
| 2100 | 24.1 | 2.4 | 9.3 |

The tablets from Example A2 of WO '675 were very hard, and the hardness did not vary across an increase of 1000 kg of compression force. This indicates that the formulation is inherently the cause of the hard tablets. Similarly, the hardness of Example B2 of WO '675 varied slightly and the consistent low hardness values indicate that this is caused by the tablet formulation. The tablets of the present formulation (Example 1) demonstrate an increased hardness as a

function of compression force, and that the tablets are sufficiently robust to be further processed.

19. Table 5 summarizes the dissolution release time profiles of Compound A from the three tablet compositions described in Tables 1 to 3.

**Table 5. Average Tablet Dissolution Results (n=6)**

| Time (minutes) | % Compound A Released | | |
|---|---|---|---|
| | WO '675 A2 (10 mg) | WO '675 B2 (10 mg) | Example 1 (10 mg) |
| 0 | 0 | 0 | 0 |
| 5 | 43 | 57 | 44 |
| 10 | 58 | 97 | 81 |
| 20 | 70 | 99 | 95 |
| 30 | 77 | 99 | 96 |
| 45 | 82 | 99 | 97 |

The dissolution data for the very hard tablets from Example A2 of WO '675 (Table 4) demonstrate that an incomplete release of the drug (82%) was achieved after 45 minutes. While the release of the drug from Example B2 of WO '675 was complete, the tablets were unacceptably soft and would not maintain integrity during further manufacturing processes. The tablets of the present formulation (Example 1) released the drug more quickly and more completely than Example A2 of WO '675 and had sufficient hardness to be coated, packaged, and shipped.

20. In summary, the presently claimed formulations as a whole solve the problems not taught by Daugan, Seth, and Butler, alone or in combination. Through these innovative formulations, the present invention provides unexpected and surprising results in the therapeutic delivery of Compound A by providing a rapid onset of the therapeutic effect and enhanced bioavailability, as well as providing tablets with uniform potency and desirable stability.

21. All statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; further, these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or document or any patent resulting therefrom.

Martha A. Kral

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Dated: 15 Dec 2005